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Inter-Agency Advisory Regarding Claims That Smoked Marijuana Is a Medicine

Claims have been advanced asserting smoked marijuana has a value in treating various medical conditions. Some have argued that herbal marijuana is a safe and effective medication and that it should be made available to people who suffer from a number of ailments upon a doctor's recommendation, even though it is not an approved drug.

Marijuana is listed in schedule I of the Controlled Substances Act (CSA), the most restrictive schedule. The Drug Enforcement Administration (DEA), which administers the CSA, continues to support that placement and FDA concurred because marijuana met the three criteria for placement in Schedule I under 21 U.S.C. 812(b)(1) (e.g., marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision). **Furthermore, there is currently sound evidence that smoked marijuana is harmful. A past evaluation by several Department of Health and Human Services (HHS) agencies, including the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA) and National Institute for Drug Abuse (NIDA), concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use. There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana.**

FDA is the sole Federal agency that approves drug products as safe and effective for intended indications. The Federal Food, Drug, and Cosmetic (FD&C) Act requires that new drugs be shown to be safe and effective for their intended use before being marketed in this country. FDA's drug approval process requires well-controlled clinical trials that provide the necessary scientific data upon which FDA makes its approval and labeling decisions. If a drug product is to be marketed, disciplined, systematic, scientifically conducted trials are the best means to obtain data to ensure that drug is safe and effective when used as indicated. Efforts that seek to bypass the FDA drug approval process would not serve the interests of public health because they might expose patients to unsafe and ineffective drug products. FDA has not approved smoked marijuana for any condition or disease indication.

A growing number of states have passed voter referenda (or legislative actions) making smoked marijuana available for a variety of medical conditions upon a doctor's recommendation. **These measures are inconsistent with efforts to ensure that medications undergo the rigorous scientific scrutiny of the FDA approval process and are proven safe and effective under the standards of the FD&C Act. Accordingly, FDA, as the federal agency responsible for reviewing the safety and efficacy of drugs, DEA as the federal agency charged with enforcing the CSA, and the Office of National Drug Control Policy, as the federal coordinator of drug control policy, do not support the use of smoked marijuana for medical purposes.**

NATIONAL INSTITUTE ON DRUG ABUSE

Research Report

SERIES

MARIJUANA *Abuse*

From the Director

In the 1970s, the baby boom generation was coming of age, and its drug of choice was marijuana. By 1979, more than 60 percent of 12th-graders had tried marijuana at least once in their lives. From this peak, the percentage of 12th-graders who had ever used marijuana decreased for more than a decade, dropping to a low of 33 percent in 1992. However, in 1993, first-time marijuana use by 12th-graders was on the upswing, reaching 50 percent by 1997. Although the percentage of 12th-graders who have experience with marijuana has remained roughly level since then, there is still reason to be concerned.¹ In 2002, an estimated 2.6 million Americans used marijuana for the first time. Roughly two-thirds of them were under age 18.² Furthermore, the marijuana that is available today can be 5 times more potent than the marijuana of the 1970s.³

The use of marijuana can produce adverse physical, mental, emotional, and behavioral changes, and - contrary to popular belief - it can be addictive. Marijuana smoke, like cigarette smoke, can harm the lungs.^{4,5,6} The use of marijuana can impair short-term memory,^{7,8} verbal skills,⁹ and judgment¹⁰ and distort perception.^{11,12} It also may weaken the immune system^{13,14,15,16} and possibly increase a user's likelihood of developing cancer.^{14,17} Finally, the increasing use of marijuana by very young teens may have a profoundly negative effect upon their development.^{9, 18, 19,20}

We hope that this research report will help make readers aware of our current knowledge of marijuana abuse and its harmful effects.

Nora D. Volkow, M.D.

Director

National Institute on Drug Abuse

Research Report Series - Marijuana Abuse

What are the acute effects of marijuana use?

When marijuana is smoked, its effects begin immediately after the drug enters the brain and last from 1 to 3 hours. If marijuana is consumed in food or drink, the short-term effects begin more slowly, usually in 1/2 to 1 hour, and last longer, for as long as 4 hours. Smoking marijuana deposits several times more THC into the blood than does eating or drinking the drug.²⁸

Within a few minutes after inhaling marijuana smoke, an individual's heart begins beating more rapidly, the bronchial passages relax and become enlarged, and blood vessels in the eyes expand, making the eyes look red. The heart rate, normally 70 to 80 beats per minute, may increase by 20 to 50 beats per minute or, in some cases, even double.¹⁵ This effect can be greater if other drugs are taken with marijuana.²⁹

As THC enters the brain, it causes a user to feel euphoric - or "high" - by acting in the brain's reward system, areas of the brain that respond to stimuli such as food and drink as well as most drugs of abuse. THC activates the reward system in the same way that nearly all drugs of abuse do, by stimulating brain cells to release the chemical dopamine.^{30,31,32}

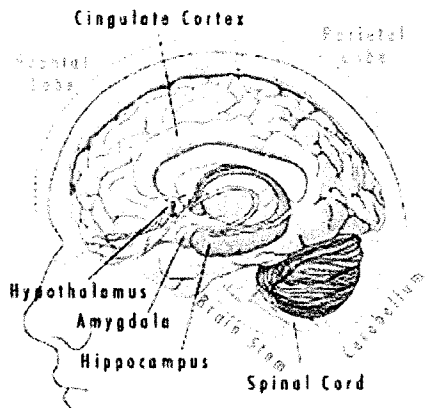
A marijuana user may experience pleasant sensations, colors and sounds may seem more intense, and time appears to pass very slowly. The user's mouth feels dry, and he or she may suddenly become very hungry and thirsty. His or her hands may tremble and grow cold. The euphoria passes after awhile, and then the user may feel sleepy or depressed. Occasionally, marijuana use produces anxiety, fear, distrust, or panic.

Heavy marijuana use impairs a person's ability to form memories, recall events (see Marijuana, Memory, and the Hippocampus), and shift attention from one thing to another.^{8,33} THC also disrupts coordination and balance by binding to receptors in the cerebellum and basal ganglia, parts of the brain that regulate balance, posture, coordination of movement, and reaction time.¹¹ Through its effects on the brain and body, marijuana intoxication can cause accidents. Studies show that approximately 6 to 11 percent of fatal accident victims test positive for THC. In many of these cases, alcohol is detected as well.^{34,35,36}

In a study conducted by the National Highway Traffic Safety Administration, a moderate dose of marijuana alone was shown to impair driving performance; however, the effects of even a low dose of marijuana combined with alcohol were markedly greater than for either drug alone.³⁷ Driving indices measured included reaction time, visual search frequency (driver checking side streets), and the ability to perceive and/or respond to changes in the relative velocity of other vehicles.

Marijuana users who have taken high doses of the drug may experience acute toxic psychosis, which includes hallucinations, delusions, and depersonalization - a loss of the sense of personal identity, or self-recognition.^{10,15} Although the specific causes of these symptoms remain unknown, they appear to occur more frequently when a high dose of cannabis is consumed in food or drink rather than smoked.

Marijuana's Effects on the Brain



When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

Brain Region	Functions Associated With Region
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Brain regions in which cannabinoid receptors are abundant

Cerebellum	Body movement coordination
Hippocampus	Learning and memory
Cerebral cortex, especially cingulate, frontal, and parietal regions	Higher cognitive functions
Nucleus accumbens	Reward
Basal ganglia Substantia nigra pars reticulata Entopeduncular nucleus Globus pallidus Putamen	Movement control

Brain regions in which cannabinoid receptors are moderately concentrated

Hypothalamus	Body housekeeping functions (body temperature regulation, salt and water balance, reproductive function)
Amygdala	Emotional response, fear
Spinal cord	Peripheral sensation, including pain
Brain stem	Sleep and arousal, temperature regulation, motor control
Central gray	Analgesia
Nucleus of the solitary tract	Visceral sensation, nausea and vomiting

How does marijuana use affect physical health?

Marijuana use has been shown to increase users' difficulty in trying to quit smoking tobacco.³⁸ This was reported in a study comparing smoking cessation in adults who smoked both marijuana and tobacco with those who smoked only tobacco. The relationship between marijuana use and continued smoking was particularly strong in those who smoked marijuana daily at the time of the initial interview, 13 years prior to the follow-up interview.

A study of 450 individuals found that people who smoke marijuana frequently but do not smoke tobacco have more health problems and miss more days of work than nonsmokers do.³⁹ Many of the extra sick days used by the marijuana smokers in the study were for respiratory illnesses.

Even infrequent marijuana use can cause burning and stinging of the mouth and throat, often accompanied by a heavy cough. Someone who smokes marijuana regularly may have many of the same respiratory problems that tobacco smokers do, such as daily cough and phlegm production, more frequent acute chest illnesses, a heightened risk of lung infections, and a greater tendency toward obstructed airways.⁴

Cancer of the respiratory tract and lungs may also be promoted by marijuana smoke.⁴ A study comparing 173 cancer patients and 176 healthy individuals produced strong evidence that smoking marijuana increases the likelihood of developing cancer of the head or neck, and that the more marijuana smoked, the greater the increase.¹⁷ A statistical analysis of the data suggested that marijuana smoking doubled or tripled the risk of these cancers.

Marijuana has the potential to promote cancer of the lungs and other parts of the respiratory tract because it contains irritants and carcinogens.⁴⁰ In fact, marijuana smoke contains 50 percent to 70 percent more carcinogenic hydrocarbons than does tobacco smoke.⁴¹ It also produces high levels of an enzyme that converts certain hydrocarbons into their carcinogenic form, levels that may accelerate the changes that ultimately produce malignant cells.⁴² Marijuana users usually inhale more deeply and hold their breath longer than tobacco smokers do, which increases the lungs' exposure to carcinogenic smoke. These facts suggest that, puff for puff, smoking marijuana may increase the risk of cancer more than smoking tobacco does.

Some adverse health effects caused by marijuana may occur because THC impairs the immune system's ability to fight off infectious diseases and cancer. In laboratory experiments that exposed animal and human cells to THC or other marijuana ingredients, the normal disease-preventing reactions of many of the key types of immune cells were inhibited.¹⁶ In other studies, mice exposed to THC or related substances were more likely than unexposed mice to develop bacterial infections and tumors.^{14,43}

One study has indicated that a person's risk of heart attack during the first hour after smoking marijuana is four times his or her usual risk.⁴⁴ The researchers suggest that a heart attack might occur, in part, because marijuana raises blood pressure and heart rate and reduces the oxygen-carrying capacity of blood.

Marijuana, Memory, and the Hippocampus

Marijuana's damage to short-term memory seems to occur because THC alters the way in which information is processed by the hippocampus, a brain area responsible for memory formation. Laboratory rats treated with THC displayed the same reduced ability to perform tasks requiring short-term memory as other rats showed after nerve cells in their hippocampus were destroyed.⁶⁶ In addition, the THC-treated rats had the greatest difficulty with the tasks precisely during the time when the drug was interfering most with the normal functioning of cells in the hippocampus.

As people age, they normally lose neurons in the hippocampus, which decreases their ability to remember events. Chronic THC exposure may hasten the age-related loss of hippocampal neurons. In one series of studies, rats exposed to THC every day for 8 months (approximately 30 percent of their lifespan), when examined at 11 to 12 months of age, showed nerve cell loss equivalent to that of unexposed animals twice their age.^{67, 68, 69}

Health Consequences of Marijuana Abuse

Acute (present during intoxication)

- Impairs short-term memory
- Impairs attention, judgment, and other cognitive functions
- Impairs coordination and balance
- Increases heart rate

Persistent (lasting longer than intoxication, but may not be permanent)

- Impairs memory and learning skills

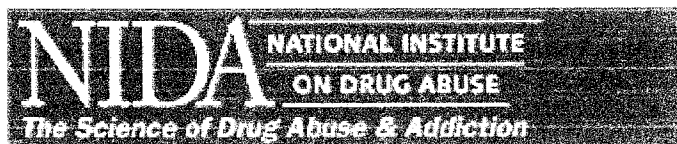
Long-term (cumulative, potentially permanent effects of chronic abuse)

- Can lead to addiction
- Increases risk of chronic cough, bronchitis, and emphysema
- Increases risk of cancer of the head, neck, and lungs

The Science of Medical Marijuana

THC, the main active ingredient in marijuana, produces effects that potentially can be useful for treating a variety of medical conditions. It is the main ingredient in an oral medication that is currently used to treat nausea in cancer chemotherapy patients and to stimulate appetite in patients with wasting due to AIDS. Scientists are continuing to investigate other potential medical uses for cannabinoids.⁷⁴

Research is underway to examine the effects of smoked marijuana and extracts of marijuana on appetite stimulation, certain types of pain, and spasticity due to multiple sclerosis. However, the inconsistency of THC dosage in different marijuana samples poses a major hindrance to valid trials and to the safe and effective use of the drug. Moreover, the adverse effects of marijuana smoke on the respiratory system^{4, 5, 6} will offset the helpfulness of smoked marijuana for some patients. Finally, little is known about the many chemicals besides THC that are in marijuana, or their possible deleterious impact on patients with medical conditions.



How does marijuana use affect school, work, and social life?

Students who smoke marijuana get lower grades and are less likely to graduate from high school, compared with their nonsmoking peers.^{20,45,46,47}

Workers who smoke marijuana are more likely than their coworkers to have problems on the job. Several studies have associated workers' marijuana smoking with increased absences, tardiness, accidents, workers' compensation claims, and job turnover. A study among postal workers found that employees who tested positive for marijuana on a pre-employment urine drug test had 55 percent more industrial accidents, 85 percent more injuries, and a 75 percent increase in absenteeism compared with those who tested negative for marijuana use.⁴⁸

Depression¹⁸, anxiety¹⁸, and personality disturbances⁵⁰ are all associated with marijuana use. Research clearly demonstrates that marijuana use has the potential to cause problems in daily life or make a person's existing problems worse. Because marijuana compromises the ability to learn and remember information, the more a person uses marijuana the more he or she is likely to fall behind in accumulating intellectual, job, or social skills. In one study of cognition, adults were matched on the basis of their performance in the 4th grade on the Iowa Test of Basic Skills. They were evaluated on a number of cognitive measures including the 12th-grade version of the Iowa Test. Those who were heavy marijuana smokers scored significantly lower on mathematical skills and verbal expression than nonsmokers.⁹

Moreover, research has shown that marijuana's adverse impact on memory and learning can last for days or weeks after the acute effects of the drug wear off.^{9,51} For example, a study of 129 college students found that among heavy users of marijuana - those who smoked the drug at least 27 of the preceding 30 days - critical skills related to attention, memory, and learning were significantly impaired, even after they had not used the drug for at least 24 hours.³³ The heavy marijuana users in the study had more trouble sustaining and shifting their attention and in registering, organizing, and using information than did the study participants who had used marijuana no more than 3 of the previous 30 days. As a result, someone who smokes marijuana once daily may be functioning at a reduced intellectual level all of the time. More recently, the same researchers showed that a group of long-term heavy marijuana users' ability to recall words from a list was impaired 1 week following cessation of marijuana use, but returned to normal by 4 weeks.⁵¹ An implication of this finding is that even after long-term heavy marijuana use, if an individual quits marijuana use, some cognitive abilities may be recovered.

Another study produced additional evidence that marijuana's effects on the brain can cause cumulative deterioration of critical life skills in the long run. Researchers gave students a battery of tests measuring problem-solving and emotional skills in 8th grade and again in 12th grade.⁵² The results showed that the students who were already drinking alcohol plus smoking marijuana in 8th grade started off slightly behind their peers, but that the distance separating these two groups grew significantly by their senior year in high school. The analysis linked marijuana use, independently of alcohol use, to reduced capacity for self-reinforcement, a group of psychological skills that enable individuals to maintain confidence and persevere in the pursuit of goals.

Marijuana users themselves report poor outcomes on a variety of measures of life satisfaction and achievement. A recent study compared current and former long-term heavy users of marijuana with a

control group who reported smoking cannabis at least once in their lives, but not more than 50 times. Despite similar education and incomes in their families of origin, significant differences were found on educational attainment and income between heavy users and the control group: fewer of the cannabis users completed college and more had household incomes of less than \$30,000. When asked how marijuana affected their cognitive abilities, career achievements, social lives, and physical and mental health, the overwhelming majority of heavy cannabis users reported the drug's deleterious effect on all of these measures.⁵³

The Body's Natural THC-Like Chemicals

THC owes many of its effects to its similarity to a family of chemicals called the *endogenous cannabinoids*, which are natural *Cannabis*-like chemicals. Because a THC molecule is shaped like these endogenous cannabinoids, it interacts with the same receptors on nerve cells, the cannabinoid receptors, that endogenous cannabinoids do, and it influences many of the same processes. Research has shown that the endogenous cannabinoids help control a wide array of mental and physical processes in the brain and throughout the body, including memory and perception, fine motor coordination, pain sensations,⁷⁰ immunity to disease, and reproduction.⁷¹

When someone smokes marijuana, THC overstimulates the cannabinoid receptors, leading to a disruption of the endogenous cannabinoids' normal function. This overstimulation produces the intoxication experienced by marijuana smokers. Over time, it may alter the function of cannabinoid receptors, which, along with other changes in the brain, can lead to withdrawal symptoms and addiction.^{60,72,73}

Can marijuana use during pregnancy harm the baby?

Research has shown that some babies born to women who used marijuana during their pregnancies display altered responses to visual stimuli, increased tremulousness, and a high-pitched cry, which may indicate problems with neurological development.^{54, 75} During the preschool years, marijuana-exposed children have been observed to perform tasks involving sustained attention and memory more poorly than nonexposed children do.^{55,56} In the school years, these children are more likely to exhibit deficits in problem-solving skills, memory, and the ability to remain attentive.^{55,56}

Is marijuana use addictive?

Long-term marijuana use can lead to addiction for some people; that is, they use the drug compulsively even though it often interferes with family, school, work, and recreational activities. According to the 2003 National Survey on Drug Use and Health (NSDUH), an estimated 21.6 million Americans aged 12 or older were classified with substance dependence or abuse (9.1 percent of the total population). Of the estimated 6.9 million Americans classified with dependence on or abuse of illicit drugs, 4.2 million were dependent on or abused marijuana.⁵⁷ In 2002, 15 percent of people entering drug abuse treatment programs reported that marijuana was their primary drug of abuse.⁵⁸

Along with craving, withdrawal symptoms can make it hard for long-term marijuana smokers to stop using the drug.⁴⁹ People trying to quit report irritability, difficulty sleeping, and anxiety.^{59,60} They also display increased aggression on psychological tests, peaking approximately 1 week after they last used the drug.⁶¹

In addition to its addictive liability, research indicates that early exposure to marijuana can increase the likelihood of a lifetime of subsequent drug problems. A recent study of over 300 fraternal and identical twin pairs, who differed on whether or not they used marijuana before the age of 17, found that those who had used marijuana early had elevated rates of other drug use and drug problems later on, compared with their twins, who did not use marijuana before age 17. This study re-emphasizes the importance of primary prevention by showing that early drug initiation is associated with increased risk of later drug problems, and it provides more evidence for why preventing marijuana experimentation during adolescence could have an impact on preventing addiction.⁶²

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Research Report

MARIJUANA

Use

What is marijuana?

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What is the scope of marijuana use in the United States?

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from the director

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